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Signed Stephen Hordley

Dated 20 March 2003

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P01/7700 0.00-0209029.8

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Request for grant of a patent
(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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Your Reference	P33037
Patent application number *(The Patent office will fill in this part)*	19 APR 2002 0209029.8
Full name, address and postcode of the or of each applicant *(underline all surnames)*	**GLAXO GROUP LIMITED** **980 GREAT WEST ROAD** **BRENTFORD** **MIDDLESEX** **TW8 9GS**
Patents ADP number *(if you know it)*	00473587006
If the applicant is a corporate body, give the country/state of its corporation	
Title of the invention	**COMPOUNDS**
Name of your agent *(if you know one)*	**JANETTE Y ROWDEN**
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**GLAXOSMITHKLINE** **980 GREAT WEST ROAD** **BRENTFORD** **MIDDLESEX** **TW8 9GS**
Patents ADP number *(if you know it)*	08366817001

If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.*	YES

See note (d))

Patents Form

Patents Form 1/77

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Continuation sheets of this form	-
Description	31
Claim(s)	5
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature JANETTE Y ROWDEN
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

LYNNE SAWKINS

020 8047 4461

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a) Notes

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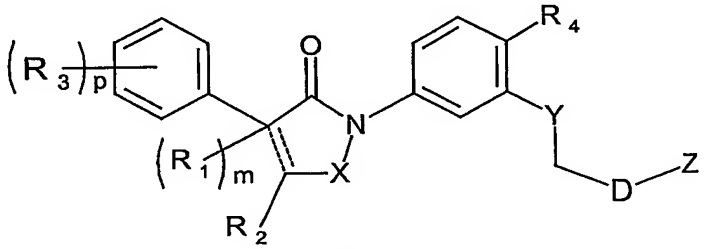
Compounds

This invention relates to novel compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment and/or prevention of CNS and other disorders.

WO 96/23783, WO 97/46699 and WO 97/48700 all disclose a series of indoline derivatives which are 5-HT_{2C} receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders.

A novel class of compounds possessing 5-HT_{2C} receptor activity has been found. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, C_{1-6}alkoxy or haloC_{1-6}alkoxy;

m is 0 when ======= is a double bond and m is 1 when ======= is a single bond;

R_2 is hydrogen, halogen, cyano, nitro, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group;

X is $-(CH_2-CH_2)-$, $-(CH=CH)-$, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, $-(CH_2-CH=CH)-$ or a group $-(CHR_5)-$ wherein R_5 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy or C_{1-6}alkylthio;

R_3 is halogen, cyano, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy, amino, mono- or di-C_{1-6}alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio or $COOR_6$, $CONR_7R_8$ or COR_9 wherein R_6, R_7, R_8 and R_9 are independently hydrogen or C_{1-6}alkyl;

p is 0, 1 or 2 or 3;

R_4 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group;

Y is oxygen, sulfur, $-CH_2-$ or NR_{10} wherein R_{10} is hydrogen or C_{1-6}alkyl;

D is a single bond, $-CH_2-$, $-(CH_2)_2-$ or -CH=CH-; and
Z is $-NR_{11}R_{12}$ where R_{11} and R_{12} are independently hydrogen or C_{1-6}alkyl, or an optionally substituted N-linked or C-linked 4 to 7 membered heterocyclic group.

The following terms, whether used alone or as part of another group are to be given the following meanings, unless otherwise stated.

The term "halogen" and its abbreviated form "halo" are used herein to describe fluorine, chlorine, bromine or iodine.

The term "alkyl" is used herein to describe a straight chain or branched fully saturated hydrocarbon group. "C_{1-6}alkyl" refers to alkyl groups having from one to six carbon atoms, including all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The term "C_{1-6}alkanoyl" refers to an alkanoyl group having from 1 to 6 carbon atoms, such as methanoyl (or "formyl"), ethanoyl (or "acetyl"), propanoyl, isopropanoyl, butanoyl, isobutanoyl, sec-butanoyl, pentanoyl, neopentanoyl, sec-pentanoyl, isopentanoyl, tertpentanoyl and hexanoyl.

The term "C_{1-6}alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group having from one to six carbon atoms, including all isomeric forms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy.

The term "C_{3-7}cycloalkyl" refers to a cycloalkyl group consisting of from 3 to 7 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Optional substituents for C_{3-7}cycloalkyl includes one or more halogen, hydroxy, oxo, C_{1-6}alkyl, cyano, CF_3, OCF_3, C_{1-6}alkoxy and C_{1-6}alkanoyl.

The term "C_{1-6}alkylthio" refers to a straight chain or branched chain alkylthio group having from one to six carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio, sec-pentylthio, n-pentylthio, isopentylthio, tert-pentylthio and hexylthio.

The term "mono- or di-C_{1-6}alkylamino" refers to an amino group which is substituted by one C_{1-6}alkyl group or an amino group which is substituted by two C_{1-6}alkyl groups, the two amino groups being the same or different. Examples of monoC1-6alkylamino include methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, sec-butylamine, tert-butylamine, pentylamine, neopentylamine, sec-pentylamine, n-pentylamine, isopentylamine, tert-pentylamine

and hexylamine. Examples of di-C1-6alkylamino include dimethylamine, diethylamine, dipropylamine, diisopropylamine, dibutylamine, diisobutylamine, disec-butylamine, ditert-butylamine, dipentylamine, dineopentylamine, dihexylamine, butylmethylamino, isopropylmethylamino, ethylisopropylamino, ethylmethylamino, etc.

The term "aryl" is used herein to describe groups such as phenyl or naphthyl, which may be optionally substituted by one or more of C_{1-6}alkyl (to form "arylC_{1-6}alkyl"), halogen, CF_3 or C_{1-6}alkoxy (to form "arylC_{1-6}alkoxy").

The terms "halo C_{1-6}alkoxy" or "haloC_{1-6}alkyl" are used to describe a C_{1-6}alkoxy or a C_{1-6}alkyl group, respectively, substituted with one or more halogens. Examples include $-CHCl_2$, $-CF_3$, $-OCF_3$, etc.

The term " heterocyclic group" is used herein to describe a stable aromatic or non-aromatic ring containing 1, 2 or 3 heteroatoms selected from nitrogen, sulphur and oxygen. Suitable examples of 4 to 7 membered heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, piperidyl, piperazinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl, azepanyl, dioxolanyl, thienyl, tetrahydrothienyl, tetrahydrofuryl, dioxanyl and dithianyl.

The term "N-linked heterocyclic group" is used herein to describe a heterocyclic groupwhich is linked to the remainder of the molecule via a nitrogen atom. Suitable examples of 4 to 7 membered N-linked heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, piperidyl, piperazinyl, morpholinyl and azepanyl.

The term "C-linked heterocyclic group" is used herein to describe a heterocyclic group which is linked to the remainder of the molecule via a carbon atom. Suitable examples of 4 to 7 membered C-linked heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, piperidyl, piperazinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl, azepanyl, dioxolanyl, thienyl, tetrahydrothienyl, tetrahyrdofuryl, dioxanyl and dithianyl.

More than one optional substituent may be present in the N-linked or C-linked heterocycle, which may be the same or different, and may be attached to any carbon atom of the heterocycle or an available nitrogen atom.

Suitable optional substituents for the N-linked or C-linked heterocycle include C_{1-6}alkyl, amino, mono- or di- C_{1-6}alkylamino, aryl, arylC_{1-6}alkyl, arylamino, hydroxy, C_{1-6}alkylamido, hydroxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, halogen, haloC1-6alkyl, a heteroaromatic group (such as indole or benzimidazole), an aromatic or non-aromatic N-linked or C-linked heterocycle or an aromatic or non-aromatic heterocycleC_{1-6}alkyl optionally substituted by C_{1-6}alkyl. Examples of aromatic or non-aromatic heterocycleC_{1-6}alkyl include heterocycle-methyl (such as pyridinyl-methyl and benzimidazolyl-methyl) and heterocycle-ethyl (such as morpholinyl-ethyl and indolyl-ethyl).

Substituents in the N-linked or C-linked heterocycle may form a bridge structure, to form a group such as for example 2-oxa-5-azabicyclo[2.2.1]heptyl. Such a bicyclic group may be further substituted by the substituents listed above. More than one substituent may be present on the same carbon atom to form spiro structures such as 1,4 and 1,5 dioxa spiro compounds.

When X is a group -(CHR_5)-, preferably R_5 is hydrogen. Preferably X is -CH_2-.

When ======= is a single bond, preferably R_1 is hydrogen, hydroxy or C_{1-6}alkoxy.

Preferably R_2 is hydrogen.

When p is 2 or 3, R_3 may be the same or different. Preferably p is 1 or 2 and R_3 is/are halogen, particularly chloro or fluoro, attached at the 3 or the 3,4-positions of the phenyl ring.

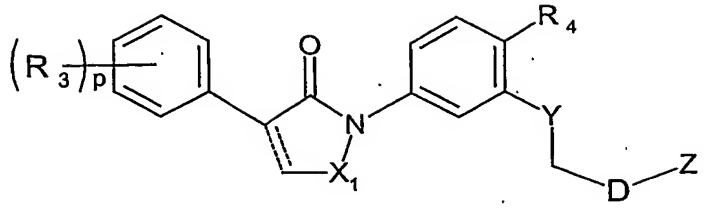
Preferably R_4 is C_{1-6}alkoxy (particularly methoxy), OCF_3, halogen or cyano.

Preferably Y is oxygen.

Preferably D is -CH_2-.

Preferably Z is an optionally substituted N-linked 4 to 7 membered heterocycle, in particular piperidyl. Preferred substituents include halogen (particularly fluoro) and C_{1-6}alkyl (particularly methyl).

Preferred compounds are compounds of formula (Ia):



(Ia)

wherein R_3, p, R_4, Y, D, Z, ======= are as defined for formula (I) and X_1 is $-CH_2-$ or -HC(OH)-. Preferred features of formula (I) also apply to formula (Ia).

Preferred compounds include:

1. 3-(3,4-Dichloro-phenyl)-3-hydroxy-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
2. 3-(3,4-Dichloro-phenyl)-3-hydroxy-1-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrrolidin-2-one
3. 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
4. 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-pyrrolidin-2-one
5. 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-3-hydroxy-pyrrolidin-2-one
6. 3-(3,4-Dichloro-phenyl)-1-(4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl)-pyrrolidin-2-one
7. 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one
8. 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one
9. 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-1,5-dihydro-pyrrol-2-one
10. 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one
11. 3-(3-Fluoro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one
12. 3-(3,4-Dichloro-phenyl)-1-(-3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-4-methoxy-phenyl)-1,5-dihydro-pyrrol-2-one
13. 3-(3-Fluoro-phenyl)-5-hydroxy-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
14. 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-5-hydroxy-pyrrolidin-2-one
15. 3-(3,4-Dichloro-phenyl)-1-(-3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-4-methoxy-phenyl)-5-hydroxy-pyrrolidin-2-one
16. 3-(3-Fluoro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one

and pharmaceutically acceptable salts thereof.

The compounds of formula (I) can form acid addition salts. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be

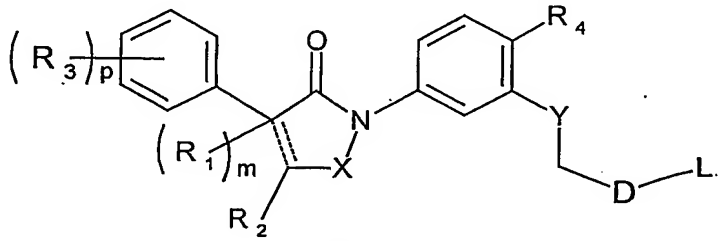
pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric or ("*cis-trans*") isomers, diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II):



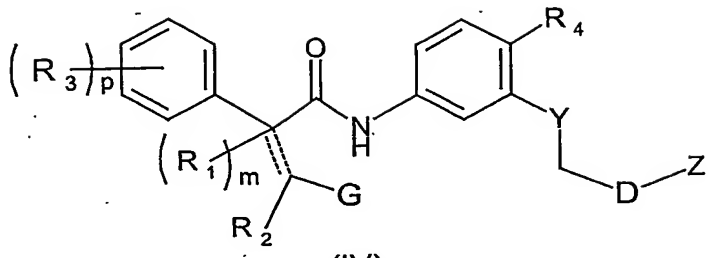
(II)

wherein R_1, R_2, R_3, R_4, m, p, X, ======, Y and D are as defined for formula (I), and L is a leaving group, with a compound of formula (III):

Z-H
(III)

wherein Z is as defined for formula (I); or

(b) cyclising a compound of formula (IV):



(IV)

wherein R_1, R_2, m, R_3, p, R4, Y, D, Z and ======= are as defined for formula (I) and G is a group -X=CH_2, wherein X is as defined for formula (I), dehydrogenated as required;

optionally followed by:

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or
- forming a pharmaceutically acceptable salt.

For the reaction of process (a), suitably L is mesylate. The reaction may take place in a solvent such as DMF in the presence of sodium iodide and potassium carbonate.

The reaction of process (b) suitably takes place in a solvent such as THF in the presence of OsO_4 and $NaIO_4$.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, a compound wherein X is -(HCOH)- may be converted to a compound wherein X is -(CH_2)- by using a suitable reducing agent such as triethylsilane-trifluoroacetic acid using dichloromethane as solvent, and a compound wherein R_1 is hydroxy may be converted to compound wherein m is 0 and ======= is a double bond by an elimination reaction in TFA.

Compounds of formulae (II), (III) and (IV) are commercially available or may be prepared according to methods described herein or may be prepared according to known methods or by analogous methods thereto.

Those skilled in the art will appreciate that it may be necessary to protect certain groups to carry out the above processes. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose);, fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate);, tabletting lubricants lubricants (e.g. magnesium stearate, talc or silica);, disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in

ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal

administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

The compounds of the present invention have affinity for the 5-HT_{2C} receptor. The affinity can be determined by assessing their ability to displace [^{3}H]-mesulergine from rat or human 5-HT_{2C} clones expressed in 293 cells *in vitro*, as described in WO 94/04533.

All the Example compounds were tested according to this assay and were found to have pKi values >5.8. Some compounds show a considerably higher affinity in the range of 7.0 to >9.0 in human cells.

The intrinsic activity of the compounds of this invention can be determined according to the [^{35}S]GTPγS functional assay which is described in WO 99/07700.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use in the treatment of certain CNS disorders such as depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example of the Alzheimer's type, vascular dementia with depressed mood, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc*), anxiety including generalised anxiety and social anxiety disorder, schizophrenia, panic disorder, agoraphobia, social phobia, epilepsy, obsessive compulsive disorder and post-traumatic stress disorder, pain (particularly neuropathic pain), migraine, memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine,

methylamphetamine) or a combination thereof, Alzheimer's disease, motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, disorders associated with spinal trauma and/or head injury such as hydrocephalus, gastrointestinal disorders such as IBS (Irritable Bowel Syndrome), Crohn's disease, ulcerative colitis, non-steroidal anti-inflammatory drug induced damage) as well as microvascular diseases such as macular oedema and retinopathy.

It is to be understood that, as used herein, the term "treatment" refers to alleviation of established symptoms as well as prophylaxis.

Thus the present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance. In particular, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of the above disorders. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a therapeutic substance in the treatment of a CNS disorder. Preferably the CNS disorder is depression and/or anxiety.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, NK-1 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention further provides a method of treatment of the above disorders in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In particular the invention provides a a method of treatment of a CNS disorder in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Preferably the disorder is depression and/or anxiety.

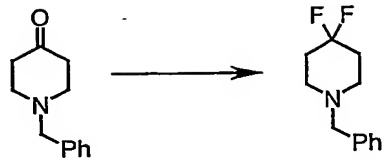
In another aspect, the invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders. In particular the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a CNS disorder. Preferably the CNS disorder is depression and/or anxiety.

The composition of the present invention may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months. When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the present invention.

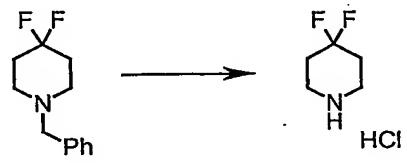
Preparation 1: 1-Benzyl-4,4-difluoro-piperidine



Procedure: *Chem. Pharm. Bull.* **1993**, *41*, **11**, 1971.

NMR (^{1}H, $CDCl_3$): δ 7.4-7.25 (m, 5H), 3.55 (s, 2H), 2.54 (m, 4H), 1.99 (m, 4H). **MS (*m/z*):** 212 $[MH]^+$

Preparation 2 : 4,4-Difluoro-piperidine hydrochloride

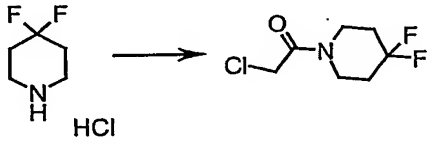


Procedure: *Chem. Pharm. Bull.* **1993**, *41*, **11**, 1971.

NMR (^{1}H, DMSO-d6): δ 9.22 (bs, 2H), 3.20 (m, 4H), 2.25 (m, 4H).

MS (*m/z*): 122 $[MH\text{-}HCl]^+$

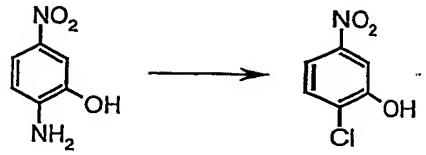
Preparation 3: 2-Chloro-1-(4,4-difluoro-piperidin-1-yl)-ethanone



Procedure: To a solution of 4,4-difluoro-piperidine hydrochloride (1120 mg, 7.13 mmol) in anh. CH_2Cl_2 (10ml) was added, at 0°C and. under N_2, TEA (2.5eq, 2.18 ml) and chloroacetyl chloride (1.1eq, 661µl). The reaction was stirred at room temperature for 1 hour. The solution was diluted with water (30 ml) and extracted with ethyl acetate (3x25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give 1128 mg of the title product (yield: 80.3%).

NMR (^{1}H, DMSO-d6): δ 4.44 (s, 2H), 3.55 (m, 4H), 2.0 (m, 4H). **MS (*m/z*):** 198 $[MH]^+$, 1Cl

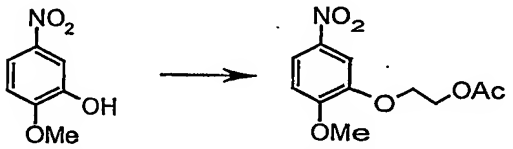
Preparation 4: 2-Chloro-5-nitro-phenol



Procedure: *J. Chem. Soc.* **1896**, *69*, 1326.

NMR (^{1}H, DMSO-d6): δ 11.3 (s, 1H), 7.75 (d, 1H), 7.66 (d, 1H), 7.64 (s, 1H).

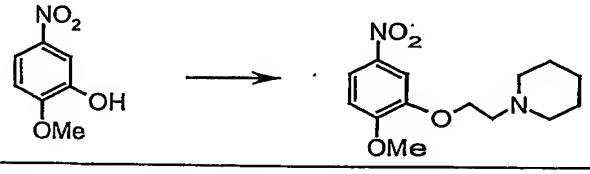
Preparation 5: Acetic acid 2-(2-methoxy-5-nitro-phenoxy)-ethyl ester



Procedure: To a solution of 2-methoxy-5-nitro-phenol (2202 mg, 13.02 mmol) in acetone (110 ml), under N_2, was added K_2CO_3 (4.45 eq., 8000 mg) and 2-bromoethyl acetate (2.1 eq, 3ml). The mixture was heated to reflux for 20 hours, filtered and then concentrated *in vacuo*. The crude product was triturated with AcOEt/cHex 1/1 (70ml) to give 2999 mg of the title product as a white solid (90.2%, mp: 120-121.3°C).

NMR (^{1}H, $CDCl_3$): δ 7.9 (dd, 1H), 7.75 (d, 1H), 6.9 (d, 1H), 4.45 (m, 2H), 4.3 (m, 2H), 3.95 (s, 3H), 2.05 (s, 3H).

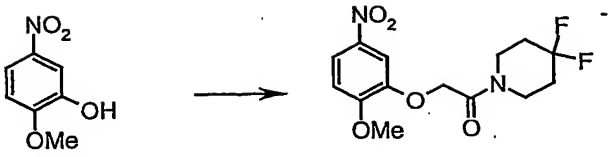
Preparation 6: 1-[2-(2-Methoxy-5-nitro-phenoxy)-ethyl]-piperidine



Procedure: To a solution of 2-methoxy-5-nitrophenol (1.5 g, 8.87 mmol) in DMF (18 ml) at room temperature were added K_2CO_3 (2.70 g, 19.52 mmol) and (1-(2-chloroethyl)piperidin hydrochloride) (1.79 g, 9.75 mmol). The suspension was stirred at room temperature for 24 hours. The suspension was diluted with water (20 ml) and extract with EtOAc (2x20 ml), the combined organic phases were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*, to obtain the title product as a yellow oil.

NMR (^{1}H, $CDCl_3$): δ 7.85 (dd, 1H), 7.75 (d, 1H), 6.90 (d, 1H), 4.20 (t, 2H), 3.90 (s, 3H), 2.80 (t, 2H), 2.45-2.60 (m, 4H), 1.55-1.65 (m, 4H) (m, 4H), 1.35-1.50 (m, 2H).
MS (*m/z*): 281[MH]$^+$.

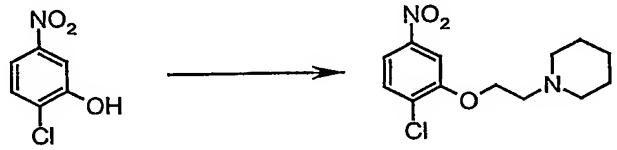
Preparation 7: 1-(4,4-Difluoro-piperidine-1-yl)-2-(2-methoxy-4-nitro-phenoxy)-ethanone



Procedure: 2-Methoxy-4-nitro-phenol (177 mg, 1.05 mmol), was dissolved in dry DMF (2 ml) under N_2. Potassium carbonate (158 mg, 1.1 eq) was added and the mixture was stirred for 15 min, then 2-chloro-1-(4,4-difluoro-piperidin-1-yl)-ethanone (228 mg, 1.1 eq) dissolved in dry DMF (3 ml) was added. After 20 hours a saturated solution of NH_4Cl was added and the mixture extracted with CH_2Cl_2 (2x25 ml). The organic phase was washed with NaOH 0.1 N (50 ml), water (50 ml), dried over Na_2SO_4 and concentrated in vacuo to give 405 mg of crude title prodcuct (mp 127-130 °C) that was utilized without further purification.

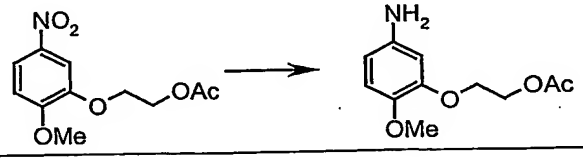
NMR (^{1}H, $CDCl_3$): δ 7.98 (dd, 1H), 7.77 (d, 1H), 6.96 (d, 1H), 4.84 (s, 2H), 3.98 (s, 3H), 3.8-3.65 (m, 4H), 2.15-1.95 (m, 4H). **MS (*m/z*):** 331 $[MH]^+$.

Preparation 8: 1-[2-(2-Chloro-5-nitro-phenoxy)-ethyl]-piperidine



NMR (^{1}H, $CDCl_3$): δ 7.84 (d, 1H), 7.81 (dd, 1H), 7.52 (d, 1H), 4.30 (t, 2H), 2.92 (t, 2H), 2.6 (m, 4H), 1.5-1.7 (m, 6H). **MS (*m/z*):** 285 $[MH]^+$, 1Cl.

Preparation 9: Acetic acid 2-(5-amino-2-methoxy-phenoxy)-ethyl ester



Procedure: To a suspension of acetic acid 2-(2-methoxy-5-nitro-phenoxy)-ethyl ester (2904 mg, 11.38 mmol) in methanol (85 ml) was added, under N_2, ammonium formate (5.4 eq, 3900 mg) and Pd/C 10% (cat, 1100 mg). The reaction was stirred at room temperature for 1.5 hours, then filtered on celite pad and concentrated to dryness *in vacuo*. The crude product was then dissolved in CH_2Cl_2 (50ml) and the organic phase was washed with brine (2x30ml) and water (1x30ml). The combined organic extracts were dried over anhydrous Na_2SO_4 filtered and concentrated to

dryness *in vacuo*. Flash chromatography of the crude product (silica gel, cHex/AcOEt 4/6) gave 2299 mg of the title product as a white foam (yield: 89.7%).

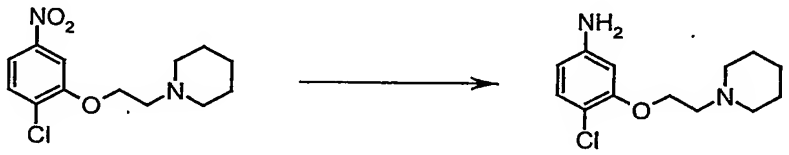
NMR (^{1}H, $CDCl_3$): δ 6.7 (dd, 1H), 6.3 (d, 1H), 6.25 (dd, 1H), 4.4 (m, 2H), 4.15 (m, 2H), 3.75 (s, 3H), 2.05 (s, 3H). **MS (*m/z*):** 226.3 $[MH]^+$.

Preparation 10: 4-Methoxy-3-(2-piperidin-1-yl)-ethoxy-phenylamine hydrochloride

Procedure: To a solution of the compound of Preparation 6 (2.30 g, 8.21 mmol) in MeOH (43.18 ml) were added a solution of NH_4Cl (5 eq, 2.20 g) in H_2O (36.83 ml) and iron (3 eq, 1.38 g). After stirring at reflux for 3 hours, the solution was concentrated *in vacuo* and the crude was tritured with CH_2Cl_2 to obtain 1.82 g of th title compound as a brown gum (yield: 76%).

(^{1}H, DMSO-d6): δ 10.4-10.0 (broad, 1H), 6.72 (d, 1H), 6.34(d, 1H), 6.20 (dd, 1H), 5.4-5.0 (broad, 2H), 4.24 (t, 2H), 3.64 (s, 3H), 3.52 (bs, 2H), 3.42 (t, 2H), 3.00 (bs, 2H), 1.9-1.3 (bs, 6H). **MS (*m/z*):** 251$[MH]^+$.

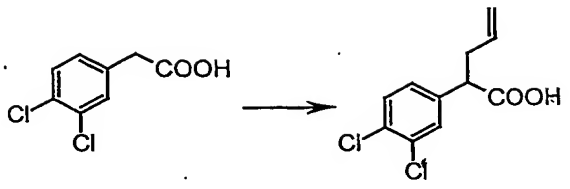
Preparation 11: 4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenylamine



Procedure: To a solution of 1-[2-(2-chloro-5-nitro-phenoxy)-ethyl]-piperidine (782 mg, 2.75 mmol) in MeOH (8 ml) were added a solution of NH_4Cl (5 eq, 735 mg) in H_2O (8 ml) and iron (3 eq, 457 mg). After stirring at reflux for 12 hours, the solution was concentrated *in vacuo* and chromatographated over silica gel (CH_2Cl_2/MeOH 85/15) to give 757 mg of the title product as a green foam (yield: 87%).

NMR (^{1}H, CD_3OD): δ 7.0 (d, 1H), 6.4 (d, 1H), 6.2 (dd, 1H), 4.25 (t, 2H), 3.35 (t, 2H), 3.25 (s, 2H), 3.15 (m, 4H), 1.8-1.5 (m, 6H). **MS (*m/z*):** 255 $[MH]^+$, 1Cl.

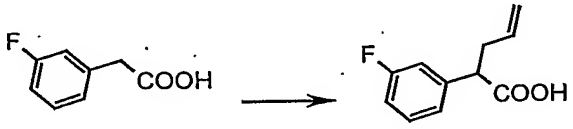
Preparation 12: 2-(3,4-Dichloro-phenyl)-pent-4-enoic acid



Procedure: A solution of 3,4-dichloro-phenylacetic acid (1.47 g, 7.17 mmol) in anh. THF (21 ml), under N_2, was treated with lithium bis(trimethylsilyl) amide (1 M solution in THF, 2.2 eq., 16 ml) at -78°C for 30 minutes before allyliodide(1.65 eq., 1.1 ml) was added. The mixture was stirred for 3 hours at room temperature and quenched with water (20 ml). The reaction mixture was acidified to pH=4 with HCl 1N. The product was extracted with ethyl acetate (2x 15ml) and the organic phase was washed with brine (1x15ml), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, AcOEt/cHex 2/8) to give 1137 mg of the title product as a pale yellow solid (81%).

NMR (^{1}H, $CDCl_3$): δ 7.4 (m, 2H), 7.15 (dd, 1H), 5.7 (m, 1H), 5.05 (m, 2H), 3.6 (t, 1H), 2.8 (m, 1H), 2.5 (m, 1H). **MS (*m/z*):** 244 $[MH]^+$ +2Cl.

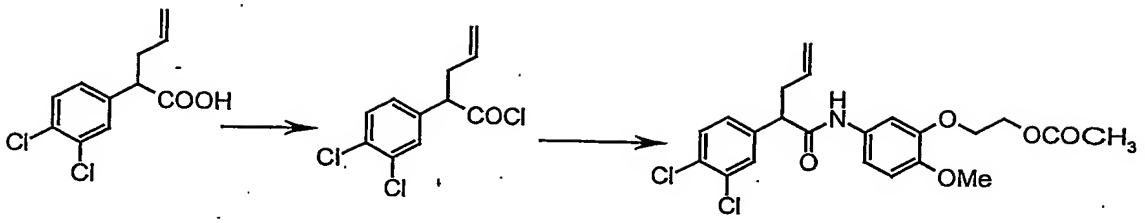
Preparation 13: 2-(3-Fluoro-phenyl)-pent-4-enoic acid



Procedure: To a solution of 3-fluorophenylacetic acid (1.0 g, 6.49 mmol) in THF (10 mL), at –78°C was added lithium bis(trimethylsilyl)amide (14.28 mmol). To solution was stirred at this temperature for 30 min and allyl bromide (0.84 mL. 9.74 mmol) was added. The solution was stirred at room temperature for 3 hours. Then the solution ws diluted with water, acidified with HCl 2 N and extracted with EtOAC (3x). The combined organic phases were dried over anhydrous Na_2SO_4 filtered and concentrated to dryness *in vacuo*. Flash chromatography of the crude product (silica gel, cHex/AcOEt 7/3) gave 1.120 g of the title product (yield = 89%, mp = 49°C)

NMR (^{1}H, DMSO-d6): δ 12.50 (bs, 1H), 7.35 (m, 1 H), 7.00-7.25 (m, 3H), 5,60-5.80 (m,1H), 4.90-5.10 (m, 1H), 3.65 (t, 1H), 2.60-2.70 (m, 1H), 2.35-2.50 (m, 1H).

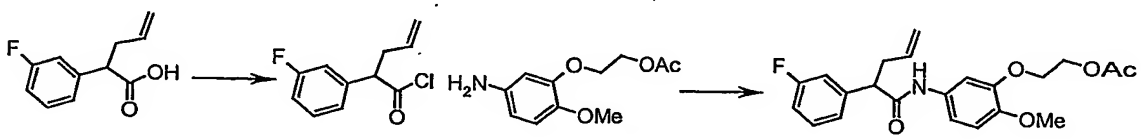
Preparation 14: Acetic acid 2-(5-[2-(3,4-dichloro-phenyl)-pent-4-enoylamine]-2-methoxy-phenoxy)-ethyl ester



Procedure: To a solution of 2-(3,4-dichloro-phenyl)-pent-4-enoic acid (222.4 mg, 0.907 mmol) in anh. CH_2Cl_2 (4 ml), under N_2, was added, at 0°C, oxalyl chloride (1.9 eq., 0.15 ml) and DMF (cat). The reaction was stirred at 0°C for 15' and at room temperature for 18 hours. The reaction mixture was concentrated to dryness *in vacuo* and the crude intermediate was then dissolved, under N_2, in anh. CH_2Cl_2 (5 ml). Acetic acid 2-(5-amino-2-methoxy-phenoxy)-ethyl ester (VVSI/6002/42/1) (1.22eq, 250 mg) and TEA (2 eq., 0.25 ml) were added to the reaction mixture at 0°C. The reaction was stirred at 0°C for 15' and at room temperature for 18 hours. The reaction mixture was concentrated to dryness *in vacuo* The crude intermediate was then dissolved in CH_2Cl_2 and the organic phase was washed with NH_4Cl sat (2x10ml) and brine (2x10ml). Flash chromatography of the crude product (silica gel, cHex/AcOEt 7/3) gave 259 mg of the title product as a white (yield: 63.1%, mp: 112.7-114.2)

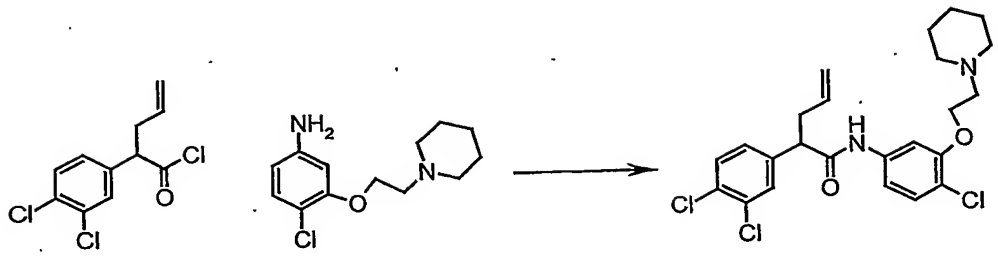
NMR (^{1}H, DMSO-d6): δ 10.02 (s, 1H), 7.60 (m, 2H), 7.36 (dd, 1H), 7.29 (d, 1H), 7.07 (dd, 1H), 6.88 (d, 1H), 5.70 (m, 1H), 5.07 (m, 1H), 4.98 (m, 1H), 4.30 (t, 2H), 4.09 (t, 2H), 3.74 (m, 1H), 3.70 (s, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.02 (s, 3H)**MS (*m/z*):** 452 $[MH]^+$+2Cl **mp**: 112.7-114°C.

Preparation 15: Acetic acid 2-(5-[2-(3-fluoro-phenyl)-pent-4-enoylamino]-2-methoxy-phenoxy)-ethyl ester



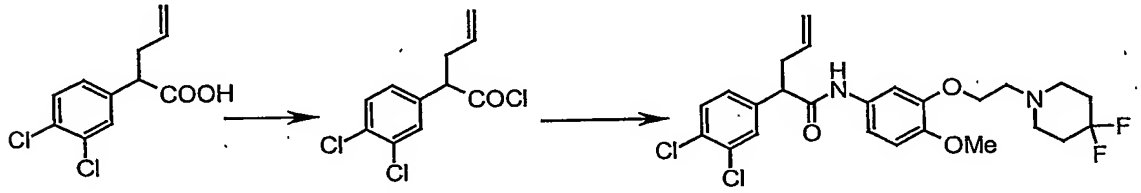
NMR (^{1}H, $CDCl_3$): δ 7.36 (d, 1H), 7.34 (m, 1H), 7.15 (d, 1H), 7.10 (dd, 1H), 7.04 (bs, 1H), 7.00 (m, 1H), 6.77-6.84 (m, 1H), 5.74 (m, 1H), 5.00-5.14 (m, 2H), 4.42 (t, 2H), 4.22 (t, 2H), 3.82 (s, 3H), 3.51 (t,1H), 2.96 (m, 1H), 2.58 (m, 1H), 2.08 (s, 3H). **MS (*m/z*):**402 $[MH]^+$. **mp** : 108.7-109.3 °C

Preparation 16: 2-(3,4-Dichloro-phenyl)-pent-4-enoic-acid [4-chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-amide



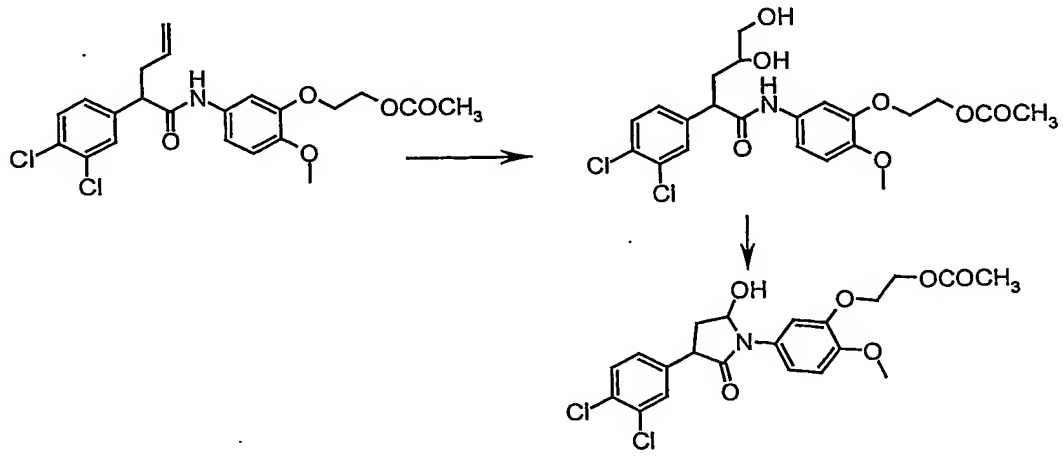
NMR (^{1}H, CD_3OD): δ 7.58 (d, 1H), 7.54 (d, 1H), 7.48 (d, 1H), 7.33 (dd, 1H), 7.27 (d, 1H), 7.0 (dd, 1H), 5.77 (m, 1H), 5.15-5.0 (m, 2H), 4.23 (t, 2H), 3.70 (t, 1H), 3.02 (t, 2H), 2.9 (m, 1H), 2.82 (m, 4H), 2.5 (m, 1H), 1.69 (m, 4H), 1.54 (m, 2H).**MS (*m/z*):** 481 [MH] +3Cl.

Preparation 17: 2-(3,4-Dichloro-phenyl)-pent-4-enoic acid (3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-4-methoxy-phenyl)-amide



NMR (^{1}H, DMSO-d6): δ 9.96 (s, 1H), 7.57 (d, 1H), 7.55 (d, 1H), 7.32 (dd, 1H), 7.25 (d, 1H), 7.01 (dd, 1H), 6.82 (d, 1H), 5.61 (m, 1H), 5.06-4.93 (m, 2H), 3.96 (m, 2H), 3.72 (t, 1H), 3.65 (s, 3H), 2.72 (t, 2H), 2.56 (t, 4H), 2.45 (m, 2H), 1.9 (m, 4H) **MS (*m/z*):** 513[MH]$^+$+2Cl.

Preparation 18: Acetic acid 2-(5-[3-(3,4-dichloro-phenyl)-5-hydroxy-2-oxo-pyrrolidine-1-yl]-2-methoxy-phenoxy)-ethyl ester



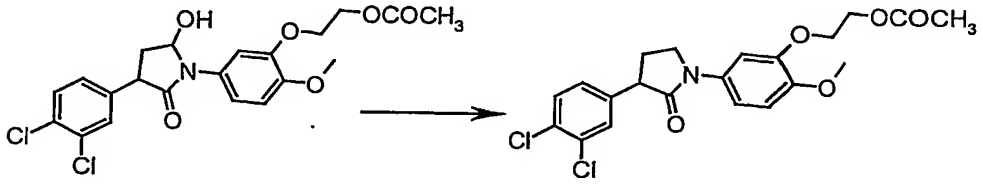
Procedure: To a solution acetic acid 2-(5-[2-(3,4-dichloro-phenyl)-pent-4-enoylamine]-2-methoxy-phenoxy)-ethyl ester (950 mg, 2.1 mmol) in acetone/H_2O 8/1 (37.5/4.6 ml) was added N-methyl-morpholine-N-oxide (2eq, 493 mg) and OsO_4 4wt% sol. in water (cat, 1 ml). The reaction was stirred at room temperature for 18 hours and then quenched with 40ml of Na_2SO_3 sat. After 15 minutes stirring the diol was extracted with ethyl acetate (2x20ml), dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude product was then dissolved in THF/H_2O 1/1 (20/20ml) and potassium periodate (1.5eq, 673.7mg) was added. The reaction was stirred at room temperature for 2 hours. The solution was diluted with water (10ml) and extracted with ethyl acetate (3x10ml). The combined organic extracts were dried over anhydrous Na_2SO_4 filtered and concentrated to dryness *in vacuo*. Flash chromatography of the crude product (silica gel, cHex/AcOEt 5/15) gave 170mg of one diastereoisomer of the title product, 227 mg of the other diastereoisomer, and 236 mg of a mixture of both as a white foam (yield: 66% in 2 steps)

(51-1)

NMR (^{1}H, DMSO-d6): δ 7.61 (d, 1H), 7.60 (d, 1H), 7.32 (dd, 1H), 7.26 (d, 1H), 7.11 (dd, 1H), 6.98 (d, 1H), 6.44 (d, 1H), 5.60 (t, 1H), 4.31 (t, 2H), 4.18 (t, 2H), 4.13 (t, 1H), 3.75 (s, 3H), 2.5-2.3 (m, 2H), 2.03 (s, 3H).
MS (*m/z*): 454 [MH] +2Cl.

(51-3)
NMR (^{1}H, DMSO-d6): δ 7.68 (d, 1H), 7.63 (d, 1H), 7.41 (dd, 1H), 7.12 (d, 1H), 6.89 (m, 2H), 6.52 (d, 1H), 5.66 (m, 1H), 4.31 (m, 2H), 4.13 (m, 2H), 3.87 (dd, 1H), 3.75 (s, 3H), 2.9 (m, 2H), 2.02 (s, 3H), 1.9 (m, 1H).

Preparation 19: Acetic acid 2-(5-[3-(3,4-dichloro-phenyl)-2-oxo-pyrrolidine-1-yl]-2-methoxy-phenoxy)-ethyl ester

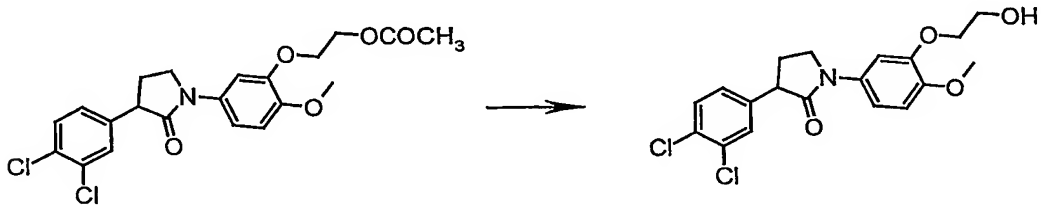


Procedure: To a solution of acetic acid 2-(5-[3-(3,4-dichloro-phenyl)-5-hydroxy-2-oxo-pyrrolidine-1-yl]-2-methoxy-phenoxy)-ethyl ester (46 mg, 0.101 mmol) and triethylsilane (1.5eq, 24μl) in CH_2Cl_2 (1ml) was added trifluoroacetic acid (10eq, 120 μl) dropwise. After stirring for 2 hours at room temperature , the solution was

concentrated *in vacuo*, and then the solution was diluted with water (10ml) and extracted with ethylacetate (3x10ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude product was purified by trituration in ether/petroleum ether 1/1 to give 30mg of the title product as a white solid (yield: 69%) (mp: 113°C)

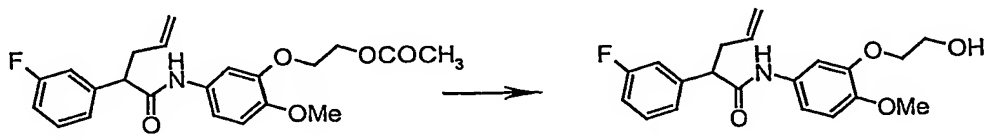
NMR (^{1}H, DMSO-d6): δ 7.62 (d, 1H), 7.61 (d, 1H), 7.47 (d, 1H), 7.33 (dd, 1H), 7.09 (dd, 1H), 6.98 (d, 1H), 4.30 (t, 2H), 4.14 (t, 2H), 3.99 (t, 1H), 3.86 (m, 2H), 3.74 (s, 3H), 2.55-2.2 (m+m, 1H+1H), 2.02 (s, 3H).
MS (*m/z*): 375 $[MH]^+$, 2Cl.

Preparation 20: 3-(3,4-Dichloro-phenyl)-1-[3-(2-hydroxy-ethoxy)-4-methoxy-phenyl]-pyrrolidine-2-one



Procedure: To a solution of acetic acid 2-(5-[3-(3,4-dichloro-phenyl)-2-oxo-pyrrolidine-1-yl]-2-methoxy-phenoxy)-ethyl ester (524 mg, 1.19 mmol) in EtOH 95% (10ml), at r.t, was added $LiOH.H_2O$ (2 eq., 100mg). After stirring for 2 hours at room temperature, the solution was concentrated *in vacuo*, and then diluted with water (10ml) and extracted with ethylacetate (3x10ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness *in vacuo*. to give 470mg of the title product (yield: 99%).
NMR (^{1}H, DMSO-d6): δ . 7.62 (s, 1H), 7.61 (d, 1H), 7.47 (d, 1H), 7.33 (dd, 1H), 7.05 (dd, 1H), 6.96 (d, 1H), 4.82 (t, 1H), 3.99 (t, 1H), 3.92 (t, 2H), 3.86 (m, 2H), 3.70 (t, 2H), 3.74 (s, 3H), 2.55-2.22 (m, 2H). **MS (*m/z*):** 396 $[MH]^+$+Cl

Preparation 21: 2-(3-Fluoro-phenyl)-pent-4-enoic acid [3-(2-hydroxy-ethoxy)-4-methoxy-phenyl]-amide

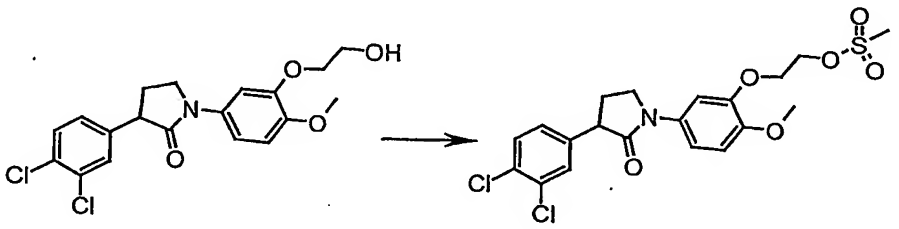


Procedure: To a solution of a compound of Preparation 15 (0.15 g, 0.37 mmol) in MeOH (1 mL) and THF (1 mL) at 45 °C was added an aqueous solution of KOH (5 M, 0.5 mL). After 15 min the mixture was cooled to 25°C. Aqueous HCl (1 M, 3 mL) and EtOAc were added. The organic layer was collected, dried ($MgSO_4$), filtered and

evaporated *in vacuo* to give the title compound (0.13 g, 0.36 mmol, 99%) as a colourless solid.

NMR (^{1}H, $CDCl_3$, 300 MHz): δ 7.27-7.40 (m, 2H), 6.93-7.15 (m, 4H), 6.71-6.85 (m, 2H), 5.62-5.80 (m, 1H), 4.98-5.11 (m, 2H), 4.05-4.11 (m, 2H), 3.86-3.90 (m, 2H), 3.80 (s, 3H), 3.50 (t, 1H), 2.90-3.02 (m, 1H), 2.46-2.60 (m, 1H), 1.91 (bs, 1H+H_2O). **MS (*m/z*):** 360 $[MH]^+$.

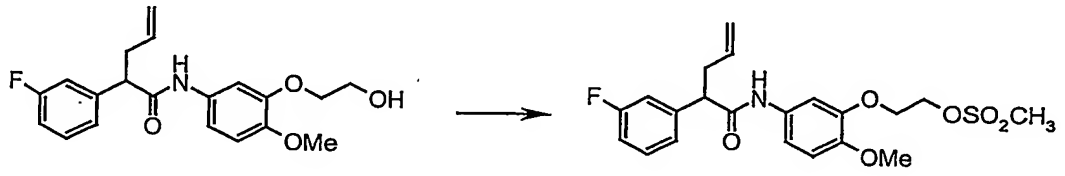
Preparation 22: Methansulfonic acid 2-(5-[3-(3,4-dichloro-phenyl)-2-oxo-pyrrolidin-1-yl]-2-methoxy-phenoxy)-ethyl ether



Procedure: To a solution of alcohol, 3-(3,4-Dichloro-phenyl)-1-[3-(2-hydroxy-ethoxy)-4-methoxy-phenyl]-pyrrolidine-2-one (470 mg, 1.18 mmol) in anh. CH_2Cl_2 (15.6 ml), at 0°C, under N_2, was added Et_3N (5 eq., 822 µl) and CH_3SO_2Cl (2eq., 180 µl). The reaction was stirred at room temperature for 3 hours. The reaction mixture was diluted with water (20 ml) and extracted with AcOEt (3x25 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* concentrated to dryness *in vacuo*. to give 560 mg of the title compound as a light yellow foam (GW 830738X) (yield: 99%).

NMR (^{1}H, DMSO-d6): δ 7.62 (m, 2H), 7.47 (d, 1H), 7.33 (dd, 1H), 7.13 (dd, 1H), 7.00 (d, 1H), 4.52 (m, 2H), 4.00 (m, 1H), 3.87 (m, 2H), 3.76 (s, 3H), 3.24 (s, 3H), 2.53 (m, 1H), 2.21 (m,1H). **MS (*m/z*):** 474 $[MH]^+$+Cl

Preparation 23: Methanesulfonic acid 2-(5-[2-(3-fluoro-phenyl)-pent-4-enoylamino]-2-methoxy-phenoxy) ethyl ester

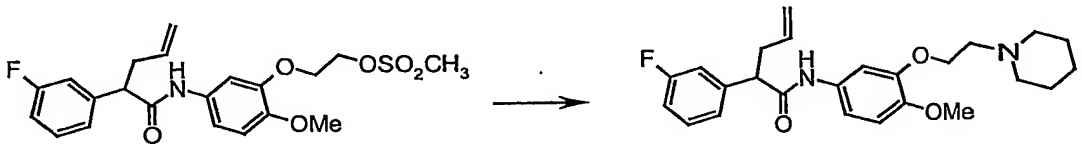


Procedure: To a partial solution of compound of Preparation 21 (0.13 g, 0.36 mmol) in DCM (2 mL) and THF (2 mL) was added *N,N*-diisopropylethylamine (0.13 mL) followed by methanesulfonyl chloride (0.037 mL) resulting in complete dissolution of the starting material. After 1.5 h water was added with stirring. After an additional 3 min the mixture was partitioned between aqueous HCl (1 M) and a 1:1 mixture of EtOAc and petroleum ether (40-60 °C). The organic layer was washed (water, brine)

and the solvents removed *in vacuo* to give the title product as a slightly yellow film (0.18 g, quant.) containing residual ethyl acetate.

NMR (^{1}H, $CDCl_3$, 300 MHz): δ 7.26-7.37 (m, 2H), 7.04-7.16 (m, 3H), 6.94-7.02 (m, 1H), 6.73-6.84 (m, 2H), 5.65-5.80 (m, 1H), 4.97-5.11 (m, 2H), 4.53-4.58 (m, 2H), 4.21-4.26 (m, 2H), 3.77 (s, 3H), 3.50 (t, 1H), 3.13 (s, 3H), 2.87-3.00 (m, 1H), 2.48-2.57 (m, 1H). **MS (*m/z*):** 438 $[MH]^+$.

Preparation 24: 2-(3-fluoro-phenyl)-pent-4-enoic acid [4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-amide



NMR (^{1}H, $CDCl_3$): δ 7.25-7.35 (m. 1H),), 7.10-7.20 (m, 3H), 6.85-7.00 (m, 2H), 6.75 (d, 1H), 5.6-5.8 (m, 1H), 4.9-5.15 (m, 2H), 4.1-4.2 (m, 3H), 3.80 (s, 3H), 3.5 (t, 1H), 2.90-3.05 (m, 2H),), 2.6-2.75 (m, 2H), 2.5-2.6 (m, 1H), 1.95-2.25 (m, 2H), 1.65-1.85 (m, 4H), 1.4-1.6 (m, 2H). **MS (*m/z*): 427** $[MH]^+$.

Preparation 25: 4,4-Difluoro-1-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-piperidine

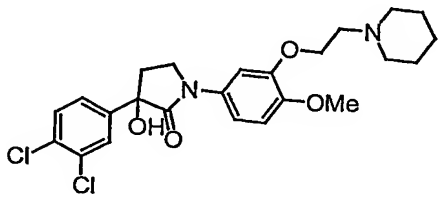
Procedure: 1-(4,4-Difluoro-piperidine-1-yl)-2-(2-methoxy-4-nitro-phenoxy)-ethanone (320 mg, 0.96 mmol) was dissolved in anh. THF (20 ml), 1M BH_3.THF (2.2eq, 2.4 ml) was added dropwise to the solution, and the mixture was heated at reflux for 5 hours. The solution was cooled to room temperature, CH_3OH (10 ml) was added, and the solvent was removed under reduced pressure. The residue was dissolved in CH_3OH (10 ml) , 6N HCl (20ml) was added, and the solution was heated to reflux for 1 hour. The CH_3OH was removed under reduced pressure and the remaining aqueous solution was made basic (pH>10) with 2.5N NaOH. The basic solution was extracted with ethyl acetate (3x20ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give 258 mg of the title product as a light yellow oil. (yield: 85%)

NMR (^{1}H, $CDCl_3$): δ 7.91 (dd, 1H), 7.77 (d, 1H), 6.89 (d, 1H), 4.19 (t, 2H), 2.90 (t, 2H), 2.71 (m, 4H), 2.01 (m, 4H).

Preparation 26: 4-[2-(4,4-Difluoro-piperidin-1-yl)-ethoxy]-3-methoxy-phenylamine

NMR (^{1}H, $CDCl_3$): δ 6.73 (d, 1H), 6.34 (d, 1H), 6.29 (dd, 1H), 4.18 (t, 2H), 3.78 (s, 3H), 3.02 (t, 2H), 2.89 (bs, 4H), 2.13 (m, 4H).

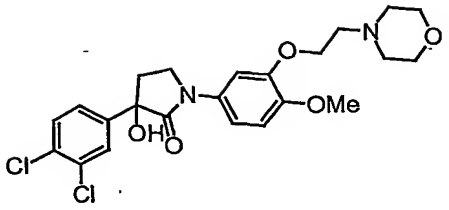
Example 1: 3-(3,4-Dichloro-phenyl)-3-hydroxy-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one



To a solution of methansulfonic acid 2-(5-[3-(3,4-dichloro-phenyl)-2-oxo-pyrrolidin-1-yl]-2-methoxy-phenoxy)-ethyl ether (103 mg, 0.216 mmol) in DMF (5ml) was added piperidine (1eq, 22µl), NaI (cat.) and K_2CO_3 (1eq, 15.5µl). The reaction mixture was heated at 60°C for 5 hours under atm N_2 and then 18 hours at room temperature in the presence of air. The reaction mixture was diluted with water (20 ml) and extracted with AcOEt (3x25 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* The crude product was purified by flash chromatography (silica gel, CH_2Cl_2/CH_3OH 18/2) to give 1.6 mg of title product as a yellow oil (3.8%).

NMR (^{1}H, DMSO-d6): δ 7.68 (d, 1H), 7.62 (d, 1H), 7.48 (d, 1H), 7.40 (dd, 1H), 7.12 (dd, 1H), 6.97 (d, 1H), 6.48 (s, 1H), 4.02 (t, 2H), 3.91-3.80 (m, 2H), 3.74 (s, 3H). 2.64 (m, 2H), 2.51-2.3 (m, 2H), 2.42 (m, 4H), 1.47-1.35 (m, 2H).. **MS (*m/z*):** 479 $[MH]^+$+ 2Cl

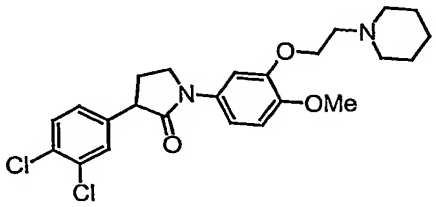
Example 2: 3-(3,4-Dichloro-phenyl)-3-hydroxy-1-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrrolidin-2-one



The product was prepared in an analogous manner as for Example 1.

NMR (^{1}H, DMSO-d6): δ 7.67 (d, 1H), 7.62 (d, 1H), 7.48 (d, 1H), 7.40 (dd, 1H), 7.12 (dd, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 4.05 (t, 2H), 3.90-3.80 (m, 2H), 3.74 (s, 3H), 3.74 (s, 3H), 3.56 (m, 4H), 2.68 (m, 2H), 2.49-2.34 (m, 2H), 2.48 (m, 4H). **MS (*m/z*):** 481 $[MH]^+$+ 2Cl

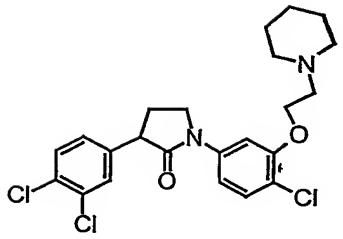
Example 3: 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one



To a solution of crude methansulfonic acid 2-(5-[3-(3,4-dichloro-phenyl)-2-oxo-pyrrolidin-1-yl]-2-methoxy-phenoxy)-ethyl ether (0.09 mmol) in DMF (2ml) was added piperidine (1eq, 9µl), NaI (cat.) and DIPEA (1eq, 15.5µl). The reaction mixture was heated at 100°C for 3 hours. The reaction mixture was diluted with water (20 ml) and extracted with AcOEt (3x25 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* The crude product was purified by flash chromatography (silica gel, CH_2Cl_2/CH3OH 18/2) to give 1.6 mg of the title product as a pale yellow solid (3.8%).

NMR (^{1}H, $CDCl_3$): δ .7.56 (d, 1H), 7.45-7.43 (m, 2H), 7.18 (dd, 1H), 6.96 (dd, 1H), 6.86 (d, 1H), 4.19 (t, 2H), 3.95-3.8 (m, 4H+2H), 2.65-2.57 (m, 1H+4H), 2.25 (m, 1H), 1.9-1.5 (m, 6H). **MS (*m/z*):** 463.4 $[MH]^+$+ 2Cl

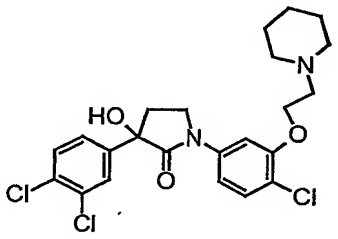
Example 4: 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-pyrrolidin-2-one



The title compound was prepared in an analogous manner to the compound of Example 3.

NMR (^{1}H, $CDCl_3$): δ 7.72 (d, 1H), 7.45 (d, 1H), 7.42 (d, 1H), 7.33 (d, 1H), 7,18 (dd, 1H), 6.90 (dd, 1H), 4.19 (t, 2H), 3.91 (dd, 2H), 3.84 (t, 1H), 2.86 (t, 2H), 2.65 (m, 1H), 2.57 (m, 4H), 2.3 (m, 1H) 1.6-1.4 (m, 6H). **MS (*m/z*):** 467 $[MH]^+$, 3Cl.

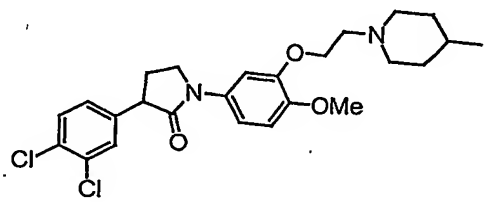
Example 5: 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-3-hydroxy-pyrrolidin-2-one



1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-pyrrolidin-2-one (26 mg, 0.055 mmol) was dissolved in DMF (1 ml), tBuOK (9 mg, 1.3 eq) was added and the mixture was stirred at room temperature in the presence of air for 30 min. A saturated solution of NH_4Cl was added and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromathography (silica gel, CH_2Cl_2/MeOH 9/1), to give 13 mg of the title product (49 % yield).

NMR (^{1}H, $CDCl_3$): δ 7.70 (d, 1H), 7.63 (m, 2H), 7.43 (d, 1H), 7.42 (dd, 1H), 7.28 (dd, 1H), 6.57 (s, 1H), 4.14 (t, 2H), 3.98 (m, 1H), 3.85 (m, 1H), 2.69 (m, 2H), 2.53 (m, 1H), 2.45 (m, 4H), 2.35 (m, 1H), 1.47-1.35 (m, 6H). **MS (*m/z*):** 483 $[MH]^+$, 3Cl.

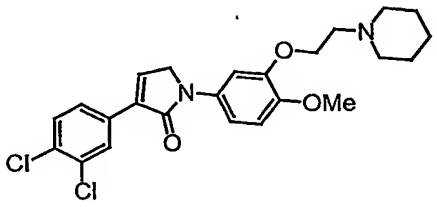
Example 6: 3-(3,4-Dichloro-phenyl)-1-(4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl)-pyrrolidin-2-one



The title compound was prepared in an analogous manner to the compound of Example 3.

NMR (^{1}H, $CDCl_3$): δ .7.57 (d, 1H), 7.44 (d+d, 1H+1H), 7.19 (dd, 1H), 6.96 (dd, 1H), 6.86 (d, 1H), 4.17 (bt, 2H), 3.90 (m, 2H), 3.83 (t, 1H), 3.86 (s, 3H), 3.00 (m, 2H). 2.84 (bt, 2H), 2.66 (m, 1H), 2.28 (m, 1H), 2.10 (m, 2H), 1.6-1.2 (m, 5H), 0.93 (d, 3H). **MS (*m/z*):** 477 $[MH]^+$+ 2Cl

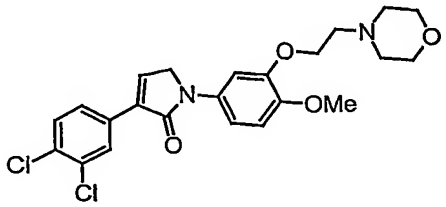
Example 7: 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one



3-(3,4-Dichloro-phenyl)-3-hydroxy-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one (17.2 mg, 0.035 mmol) was dissolved in concentrated hydrochloric acid (1.7 ml). The reaction was heated at 40°C for 3 hours, and then concentrated to dryness *in vacuo*. A solution of saturated $NaHCO_3$ was added until pH>7 and the product was extracted with ethylacetate (2x10ml). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude product was purified by flash chromatography (silica gel, AcOEt/CH_3OH 4/6) to give 11.8 mg of title product as a brown oil (55.2%).

NMR (^{1}H, $CDCl_3$): 8.05 (d, 1H), 7.78 (d, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.31 (t, 1H), 7.04 (dd, 1H), 6.88 (d, 1H), 4.45 (d, 2H), 4.20 (t, 2H), 3.87 (s, 3H). 2.85 (t, 2H), 2.54 (m, 4H), 1.62 (m, 4H), 1.45 (m, 2H). **MS (*m/z*):** 461.1 $[MH]^+$+2Cl

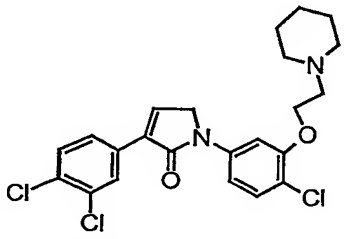
Example 8: 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one



The product was prepared in an analogous manner to Example 7.

NMR (^{1}H, $CDCl_3$): δ . 8.04 (d, 1H), 7.77 (dd, 1H), 7.72 (d, 1H), 7.48 (d, 1H), 7.31 (t, 1H), 6.96 (dd, 1H), 6.88 (d, 1H), 4.45 (d, 2H), 4.21 (t, 2H), 3.86 (s, 3H), 3.74 (m, 4H), 2.87 (t, 2H), 2.60 (m, 4H). **MS (*m/z*):** 463 $[MH]^+$+ 2Cl

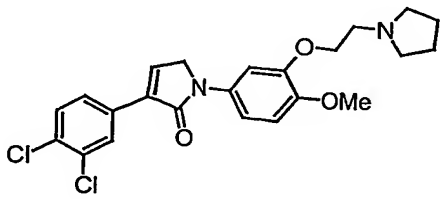
Example 9: 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-1,5-dihydro-pyrrol-2-one



1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-5-hydroxy-pyrrolidin-2-one (51 mg, 0.1 mmol) was dissolved in TFA (1 ml). The reaction mixture was stirred at room temperature for 6 hours, then concentrated in vacuo. A saturated solution of $NaHCO_3$ was added and the mixture was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromathography over silica gel (CH_2Cl_2/MeOH 95/5) to give 29 mg of the title product as a colorless oil (yield: 60 %).

NMR (^{1}H, $CDCl_3$): δ 8.0 (d, 1H), 7.83 (d, 1H), 7.73 (dd, 1H), 7.46 (d, 1H), 7,32 (d, 1H), 7.30 (m, 1H), 6.96 (dd, 1H), 4.43 (d, 2H), 4.21 (t, 2H), 2.85 (t, 2H), 2.56 (m, 4H), 1.5-1.4 (m, 6H). **MS (*m/z*):** 465 $[MH]^+$, 3Cl.

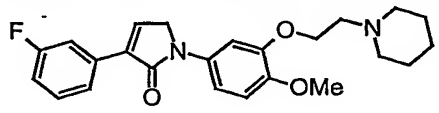
Example 10: 3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one



The title product was prepared in an analogous manner to Example 7.

NMR (^{1}H, $CDCl_3$): δ .8.06 (d, 1H), 7.78 (dd, 1H), 7.64 (d, 1H), 7.49 (d, 1H), 7.32 (t, 1H), 7.05 (dd, 1H), 6.89 (d, 1H), 4.45 (d, 2H), 4.22 (t, 2H), 3.87 (s, 3H), 2.99 (t, 2H), 2.68 (m, 4H), 1.83-1.77 (m, 4H). **MS (*m/z*):** 447 $[MH]^+$+ 2Cl

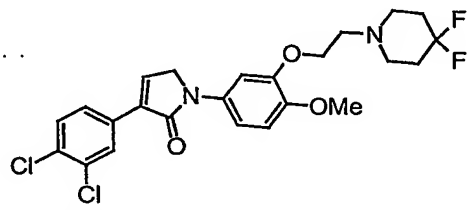
Example 11: 3-(3-Fluoro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one



The title compound was prepared in an analogous manner to the compound of Example 3.

NMR (^{1}H, $CDCl_3$): δ 7.55-7.70 (m, 3H), 7.25-7.40 (m, 2H), 6.95-7.10 (m, 2H), 6.85 (d, 1H), 4.40 (d, 2H), 4.10-4.20 (m, 2H), 3.85 (s, 3H), 2.85 (t, 2H), 2.45-2.60 (m, 4H), 1.55-1.70 (m, 4H), 1.35-1.50 (m, 2H). **MS (*m/z*):** 411[MH]$^+$.

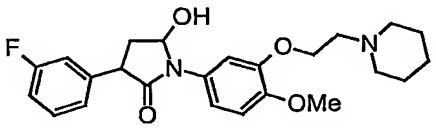
Example 12: 3-(3,4-Dichloro-phenyl)-1-(-3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-4-methoxy-phenyl)-1,5-dihydro-pyrrol-2-one



The title compound was prepared in an analogous manner to the compound of Example 3.

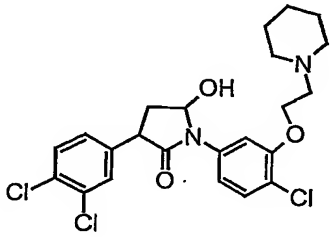
NMR (^{1}H, $CDCl_3$): δ 8.06 (d, 1H), 7.78 (dd, 1H), 7.76 (d, 1H), 7.50 (d, 1H), 7.33 (t, 1H), 6.99 (bd, 1H), 6.90 (d, 1H), 4.44 (d, 2H), 4.22 (m, 2H), 3.87 (s, 3H), 2.95 (m, 2H), 2.75 (m, 4H), 2.05 (m, 4H). **MS (*m/z*):** 497.3 [MH]$^+$+2Cl

Example 13: 3-(3-Fluoro-phenyl)-5-hydroxy-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one



To a solution of 2-(3-fluoro-phenyl)-pent-4-enoic acid [4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-amide(85 mg, 0.2 mmol) in THF/H_2O (5/1, 4 mL) was added OsO_4 (4% wt in water, 0.02 mmol) and $NaIO_4$ (86 mg, 0.4 mmol). After 18 hours the suspension was diluted with water and the aqueous phase was extracted with EtOAc (2x). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude was purified by flash chromatography (CH_2Cl_2/MeOH/ NH_4OH 95/5/0.5) to give 65 mg of title product as a brown oil. (y = 75%) MS (*m/z*): 29[MH]$^+$.

Example 14: 1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-5-hydroxy-pyrrolidin-2-one



The title compound was prepared in an analogous manner to the compound of Example 13. Two isomers A) and B) are present in 1:2 ratio.

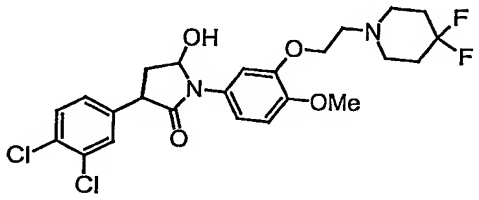
NMR (^{1}H, DMSO-d6):

A) δ 7.70-7.10 (m, 6H), 6.58 (d, 1H), 4.25 (t, 1H), 5.74 (m, 1H), 4.13 (bs, 2H), 2.63 (bs, 2H), 2.3-2.5 (m, 2H), 1.36-1.50 (bs, 10H).

B) δ 7.70-7.10 (m, 6H), 6.64 (d, 1H), 5.81 (m, 1H), 4.13 (bs, 2H), 3.93 (m, 1H), 2.63 (bs, 2H), 2.92 (m, 1H), 1.93 (m, 1H), 1.36-1.50 (bs, 10H).

MS (*m/z*): 454 [MH] +2Cl.

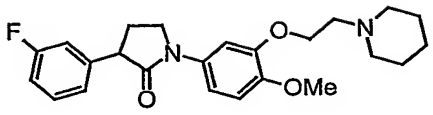
Example 15: 3-(3,4-Dichloro-phenyl)-1-(-3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-4-methoxy-phenyl)-5-hydroxy-pyrrolidin-2-one



The title compound was prepared in an analogous manner to the compound of Example 13.

NMR (^{1}H, DMSO-d6): δ 7.7-7.6 (d, 1H), 7.6 (d, 1H), 7.4-7.3 (dd, 1H), 7.25-7.12 (d, 1H), 7.10-6.95 (dd, 1H), 6.9 (d, 1H), 6.55-6.43 (d, 1H), 5.66-5.60 (m, 1H), 4.03 (t, 2H), 4.2-3.85 (m, 1H), 3.74 (s, 3H), 2.77 (t, 2H), 2.9-2.43 (m, 2H), 2.62 (m, 4H), 1.94 (m, 4H). **MS (*m/z*):** 515 $[MH]^+$+ 2Cl

Example 16: 3-(3-Fluoro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one

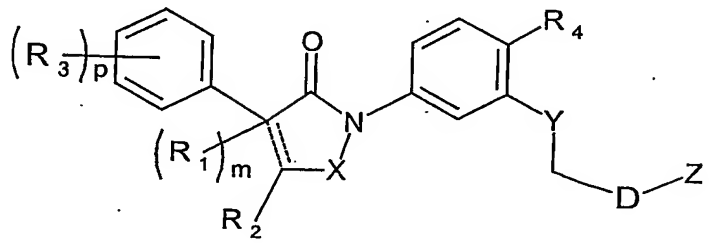


The title compound was prepared in an analogous manner to the compound of Example 3.

NMR (^{1}H, $CDCl_3$): δ 7.56 (d, 1H), 7.30 (m, 1H), 7.08 (d, 1H), 7.02 (m, 1 H), 6.95 (m, 1H), 6.93 (dd, 1H), 6.83 (d, 1H), 4.16 (t, 2H), 3.9-3.8 (m, 3H), 3.82 (s, 3H), 2.84 (t, 2H), 2.64 (bs, 4H), 2.62 (m, 1H), 2.24 (m, 1H), 1.60 (m, 4H), 1.43 (m, 2H). **MS (*m/z*):** 413$[MH]^+$.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, C_{1-6}alkoxy or haloC_{1-6}alkoxy;

m is 0 when ======= is a double bond and m is 1 when ======= is a single bond;

R_2 is hydrogen, halogen, cyano, nitro, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group;

X is $-(CH_2-CH_2)-$, $-(CH=CH)-$, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, $-(CH_2-CH=CH)-$ or a group $-(CHR_5)-$ wherein R_5 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy or C_{1-6}alkylthio;

R_3 is halogen, cyano, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy, amino, mono- or di-C_{1-6}alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio or $COOR_6$, $CONR_7R_8$ or COR_9 wherein R_6, R_7, R_8 and R_9 are independently hydrogen or C_{1-6}alkyl;

p is 0, 1 or 2 or 3;

R_4 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group;

Y is oxygen, sulfur, $-CH_2-$ or NR_{10} wherein R_{10} is hydrogen or C_{1-6}alkyl;

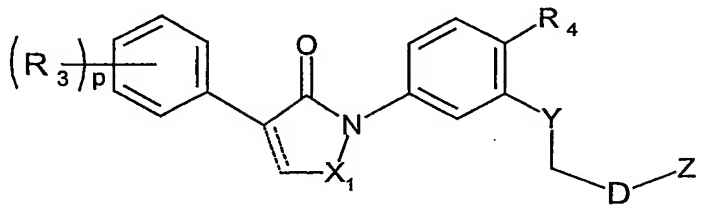
D is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-CH=CH-$; and

Z is $-NR_{11}R_{12}$ where R_{11} and R_{12} are independently hydrogen or C_{1-6}alkyl, or an optionally substituted N-linked or C-linked 4 to 7 membered heterocyclic group.

2. A compound as claimed in claim 1, wherein X is $-CH_2-$.

3. A compound as claimed in claim 1 or claim 2, wherein when ======= is a single bond, R_1 is hydrogen, hydroxy or C_{1-6}alkoxy.

4. A compound as claimed in claim 1 having the following formula (Ia):



(Ia)

wherein R_3, p, R_4, Y, D, Z, ======= are as defined for formula (I) and X_1 is $-CH_2-$ or -HC(OH)-.

5. A compound as claimed in any of claims 1-4, wherein p is 1 or 2 and R_3 is/are halogen, particularly chloro or fluoro, attached at the 3 or the 3,4-positions of the phenyl ring.

6. A compound as claimed in any of claims 1-5, wherein R_4 is C_{1-6}alkoxy (particularly methoxy), OCF_3, halogen or cyano.

7. A compound as claimed in any of claims 1-6, wherein D is $-CH_2-$.

8. A compound as claimed in any of claims 1-7, wherein Y is oxygen.

9. A compound as claimed in any of claims 1-8, wherein Z is an optionally substituted N-linked 4 to 7 membered heterocycle.

10. A compound as claimed in claim 9, wherein Z is piperidyl.

11. A compound as claimed in claim 1 which is:

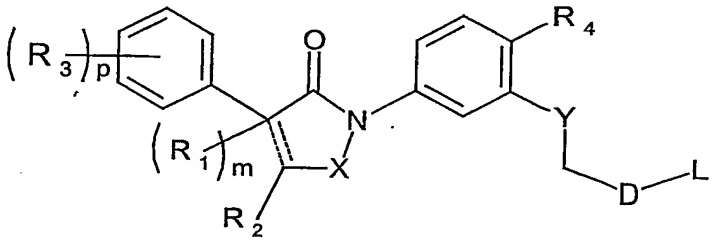
3-(3,4-Dichloro-phenyl)-3-hydroxy-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
3-(3,4-Dichloro-phenyl)-3-hydroxy-1-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrrolidin-2-one
3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-pyrrolidin-2-one
1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-3-hydroxy-pyrrolidin-2-one
3-(3,4-Dichloro-phenyl)-1-(4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl)-pyrrolidin-2-one
3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one
3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one

1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-1,5-dihydro-pyrrol-2-one
3-(3,4-Dichloro-phenyl)-1-[4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one
3-(3-Fluoro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrol-2-one
3-(3,4-Dichloro-phenyl)-1-(-3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-4-methoxy-phenyl)-1,5-dihydro-pyrrol-2-one
3-(3-Fluoro-phenyl)-5-hydroxy-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
1-[4-Chloro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-(3,4-dichloro-phenyl)-5-hydroxy-pyrrolidin-2-one
3-(3,4-Dichloro-phenyl)-1-(-3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-4-methoxy-phenyl)-5-hydroxy-pyrrolidin-2-one
3-(3-Fluoro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one

or a pharmaceutically acceptable salt thereof.

12. A process for the preparation of a compound as defined in any of claims 1-11, which process comprises:

(a) reacting a compound of formula (II):



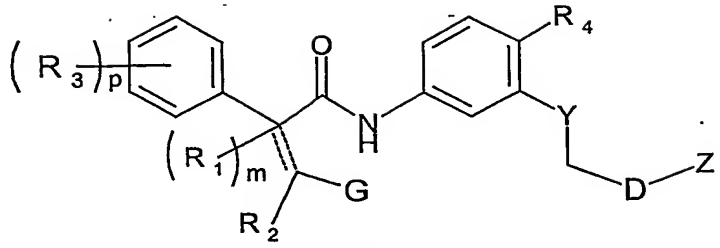
(II)

wherein R_1, R_2, R_3, R_4, m, p, X, ⁼⁼⁼⁼⁼⁼⁼, Y and D are as defined for formula (I), and L is a leaving group, with a compound of formula (III):

Z-H
(III)

wherein Z is as defined for formula (I); or

(b) cyclising a compound of formula (IV):



(IV)

wherein R_1, R_2, m, R_3, p, R4, Y, D, Z and ======= are as defined for formula (I) and G is a group $-X=CH_2$, wherein X is as defined for formula (I), dehydrogenated as required;

optionally followed by:

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or
- forming a pharmaceutically acceptable salt.

13. A pharmaceutical composition comprising a compound as defined in any of claims 1-14 and a pharmaceutically acceptable carrier or excipient.

14. A process for preparing a pharmaceutical composition as defined in claim 13, the process comprising mixing a compound a compound as defined in any of claims 1-14 and a pharmaceutically acceptable carrier or excipient.

15. A compound as defined in any of claims 1-11 for use as a therapeutic substance.

16. A compound as defined in any of claims 1-11 for use in the treatment of a CNS disorder.

17. A compound as defined in any of claims 1-11 for use in the treatment of depression and/or anxiety.

18. A method of treatment of CNS disorder in a mammal including a human, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound as defined in any of claims 1-11.

19. A method of treatment of depression and/or anxiety in a mammal including a human, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound as defined in any of claims 1-11.

20. Use of a compound as defined in any of claims 1-11 in the manufacture of a medicament for use in the treatment of a CNS disorder.

21. The use of a compound as defined in any of claims 1-11 in the manufacture of a medicament for use in the treatment of depression and/or anxiety.